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CORRESPONDENCE

Letters to the Editor

Brugada Syndrome or Brugada Electrocardiogram?

We read with great interest the paper by Benito et al. (1) from the Brugada group. The authors confirm that important differences exist between men and women regarding the clinical picture and outcome in patients with Brugada syndrome. In general, in men the clinical picture appears more severe and the outcome is worse. Although this may seem presumptuous, we wonder if all subjects in this study truly had Brugada syndrome, in particular the women. From the paper, it reads as if the diagnosis "Brugada syndrome" is synonymous with the presence of a type-1 electrocardiogram (ECG) (coved-type, either spontaneously or after pharmacologic provocation with a sodium-channel blocker). It is not mentioned whether additional clinical features were required for the diagnosis. According to the consensus statement (2), in addition to a "Brugada ECG" (type-1 ECG), for Brugada syndrome to be definitely diagnosed at least 1 of the following clinical features is required: documented ventricular fibrillation or polymorphic ventricular tachycardia, a family history of sudden death at <45 years of age, coved-type ECGs in family members, inducibility of ventricular tachycardia with programmed electrical stimulation, syncope, or nocturnal agonal respiration. In other words, a Brugada ECG is not sufficient to diagnose Brugada syndrome, and this is a very important point both in clinical practice and in scientific studies. When applying the above criteria to the study by Benito et al. (1), some uncertainty remains. According to Table 2 in their paper (1), in women syncope was present "only" in 15%, aborted sudden cardiac death in 1%, a history of sudden cardiac death in 45%, and programmed electrical stimulation was performed in 81% with inducibility in 12%. If anything, these figures do not add up to 100%. Of note, there was also a difference in the baseline ECG; as many as 62% of the women had a normal or type-3 ECG as opposed to only 25% of the men. Obviously, in subjects in whom the diagnosis of Brugada syndrome is not firmly established, a mild clinical picture and a good outcome can be expected.

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Reply

We thank Dr. van den Berg and colleagues for their interest in our article (1) and their valuable comments, which raise important issues regarding the diagnosis of Brugada syndrome. Indeed, a syndrome requires a constellation of symptoms and signs for diagnosis, and a single electrocardiographic finding does not define a syndrome. Dr. van den Berg and colleagues do certainly realize that Brugada syndrome is no longer a syndrome but a disease. After the description of the first mutation in the sodium channel causing Brugada syndrome (2), a multitude of other mutations in the sodium and other channels have been described. It is clear that the consensus report from 2005 (3) is more than outdated and an update is urgently required in terms of both diagnosis and therapeutic approach.

The definite phenotypic manifestation of the Brugada syndrome is the presence of a type-1 electrocardiogram (ECG), either spontaneously or after sodium-blocker challenge. Given that even the sole presence of the ECG pattern has been proven to entail a risk of sudden cardiac death, this was the only prerequisite required in all of our 384 patients included in the study, as stated in the article (1). However, in reply to Dr. van den Berg and colleagues, we must say that most of our patients, both men and women and in similar proportions (82.4% vs. 89.3%, respectively, $p = 0.06$), did fulfill the II Consensus Report definition of Brugada syndrome. Therefore, the better prognosis in women cannot be explained because of their lower rate of "confirmed diagnosis" according to the consensus. As can be drawn from our article, in addition to the type-1 ECG, 66 of the 272 male patients (24.3%) also had symptoms, 82 (30.1%) had a family history of early sudden death, and 84 (31.9%) had documented ventricular fibrillation either spontaneous or inducible at the time of diagnosis. Because these clinical variables tended to meet within the same individual, they resulted in a total of 148 (54.4%) patients. Additionally, in 74 (27.2%) more men, a type-1 ECG was documented in at least 1 family member. Therefore, at the time of their first evaluation, 222 of 272 patients (81.7%) had a confirmed diagnosis of Brugada syndrome according to the II Consensus definition. On the other hand, a total of 100 of 112 female patients (89.3%) fulfilled the Consensus criteria of Brugada syndrome (62 [55.4%] because of symptoms, family history of sudden death, documented ventricular fibrillation, or a combination, and 38 [33.9%] because of none of the others and a presence of type-1 ECG in family members). Importantly, among the 62 patients (50 men and 12 women) who did not meet the II Consensus definition

of Brugada syndrome at the time of first evaluation, 2 men experienced sudden death in follow-up, increasing the total of men with "confirmed diagnosis" to 224 (82.4%). The occurrence of life-threatening events in patients not fulfilling the clinical criteria proposed by the consensus attests to the need to interpret with caution the definition of Brugada syndrome, and also reminds us of the importance of following up all patients even when a type-1 ECG pattern is found in isolation.

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Left Dominant Arrhythmogenic Cardiomyopathy

A New Clinical Entity Without a Typical Substrate of Myocardial Damage

We read with interest the paper by Sen-Chowdhry et al. (1) about left dominant arrhythmogenic cardiomyopathy (LDAC). The investigators "highlight the interrelation of LDAC and arrhythmogenic right ventricular cardiomyopathy (ARVC) within the same disease spectrum and provide a composite profile of this entity" (1). The investigators identify the salient clinical features of LDAC: unexplained ventricular arrhythmia of left ventricular origin, isolated (infero)lateral T-wave inversion, mild left ventricular dilation and/or systolic impairment, and myocyte loss with fibrofatty or fibrotic replacement. Additionally, the involvement (segmental dilatation and/or wall motion abnormalities) of the right ventricle (RV) showed an important role in the diagnosis of LDAC.

On the basis of myocardial damage, the investigators illustrated 2 phenotypes of LDAC: a fibrofatty and a pure fibrotic form. Therefore, the identification of myocardial damage by histology and/or cardiac magnetic resonance with late gadolinium enhancement added with clinical manifestation of this disease plays a main role in the diagnosis of LDAC.

However, LDAC shows controversial points, particularly in its morphological features. We believe that LDAC is an under-recognized entity because it has many morphological features overlapping with those of other cardiomyopathies, particularly with dilated cardiomyopathy (DCM), biventricular form ARVC, and inflammatory cardiomyopathy (myocarditis).

The investigators suggest differentiating the LDAC phenotype from DCM on the basis of prominent RV abnormalities; however, recognizing "prominent RV abnormalities added with left ventricular involvement" as a diagnostic method for LDAC with respect to the biventricular form of ARVC can be very difficult.

Furthermore, the investigators suggest the localization of myocardial damage (fibrofatty or fibrotic tissue) as an aid to diagnosis. To distinguish these 2 entities (LDAC and DCM), they recommend the epicardial pattern of damage (late gadolinium enhancement) as indicating a suspicion of LDAC, whereas midventricular damage can be observed in both. Nevertheless, the epicardial damage is an unspecific pattern observed in many cardiomyopathies, such as myocarditis, sarcoidosis, Anderson-Fabry disease, and Chagas disease.

According to the investigators, fibrofatty replacement likely represents a nonspecific reparative process. This theory is confirmed by lipomatous metaplasia observed in the context of a myocardial infarction; the lipomatous metaplasia is caused by substitution of muscle fibers with fibrofatty tissue (2).

Recent studies suggest that the LDAC phenotype is the result of chronic myocarditis (3). However, the investigators attribute the myocardial inflammation in the setting of LDAC to a reactive unspecific consequence of loss of myocyte caused by compromised intercellular adhesion and intermediate filament function attributable to mutation in desmosomal genes. On the contrary, Bowles et al. (4) have identified the viral genome in the myocardium of ARVC; therefore, it is also possible that a genetic profile of diseased myocardium has increased the susceptibility to a viral infection that can eventually play a role in the clinical manifestations of the disease (5). Therefore, the role of inflammation in LDAC pathogenesis remains unknown.

Finally, we concur with the view of Sen-Chowdhry et al. (1) that the results described in their article add important clinical features to facilitate the diagnosis of LDAC.

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